

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

22 OCT 2005

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/039766

International filing date (day/month/year)
15.12.2004

Priority date (day/month/year)
22.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07D409/14, C07D401/04, C07D213/82, C07D213/78, A61K31/4427, A61K31/44

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/US2004/039766

IP20 Rec'd PCT/PTO 31 MAY 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/039766

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-4 (part), 5,6,7-25 (part)

because:

- ☒ the said international application, or the said claims Nos. 19-23,25 (I.A.) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-4 and 7-25 (part) ,5,6
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/039766

Box No. V Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	8,14-25
	No: Claims	1-4,7,9-13
Inventive step (IS)	Yes: Claims	1-4,7-25
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-18,24
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/039766

III NON-ESTABLISHMENT

1. Claims 19-23 and 25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
2. Present claim 1 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Furthermore, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). An initial search restricted to the compound group (Ib) as disclosed on page 12 of the description which covers the claimed examples still revealed over 500 structures potentially relevant for the assessment of novelty. For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds (Ib) wherein ring B denotes a pyridine ring, substituted in alpha-position by o-ph.

V REASONED STATEMENT

It is noted that no examination will be carried out for unsearched matter (Rule 66.1(e) PCT).

1. PRIOR ART

The documents cited in the International Search Report

D1: WO 02/38544 A (ELI LILLY AND COMPANY; JESUDASON, CYNTHIA,

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
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International application No.

PCT/US2004/039766

DARSHINI; SALL, DANIEL, JON) 16 May 2002 (2002-05-16)
D2: WO 00/40560 A (FUJISAWA PHARMACEUTICAL CO., LTD; TANIGUCHI,
KIYOSHI; SAKURAI, MINORU;) 13 July 2000 (2000-07-13)
D3: WO 98/09625 A (ELI LILLY AND COMPANY; CROWELL, THOMAS, A;
EVRARD, DEBORAH, A; JONES,) 12 March 1998 (1998-03-12)
have been considered for the examination procedure.

2. NOVELTY

The subject-matter of Claims 1-4,7 and 9-13 is anticipated by D1 (Article 33(2) PCT). On page 32, D1 discloses the intermediate amines 6,7 and 10 which are covered by the mentioned claims.

Due to the definition of R1 and R2 which does not include OH groups, the claimed object is novel vs D2 and D3.

3. INVENTIVE STEP

The closest state of the art for the present application is represented by D1, D2 and D3. All these documents are appropriate in the treatment of diabetes and obesity. The present compounds are, however, not $\beta 3$ antagonists but opioid antagonists with a different pharmacological profile. The compounds differ in the presence of an OH group within R1 and R2, in the additional presence of halogen or hydroxy (D2; within present R3,R3') or the amide group (D1; present C(W)=E) . A skilled person would thus not have arrived at the present compounds without inventive ingenuity.

4. INDUSTRIAL APPLICABILITY

No objection.

No objection for Claims 1-18 and 24. For the assessment of the present Claims 19-23 and 25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as

industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI CERTAIN DOCUMENTS CITED

- D1: WO 2004/026305 A (ELI LILLY AND COMPANY; BLANCO-PILLADO, MARIA-JESUS; CHAPPELL, MARK, DO) 1 April 2004 (2004-04-01)
- D2: WO 2004/080968 A (ELI LILLY AND COMPANY; PEDREGAL-TERCERO, CONCEPCION; SIEGEL, MILES, GO) 23 September 2004 (2004-09-23)
- D3: WO 2004/080996 A (ELI LILLY AND COMPANY; BLANCO-PILLADO, MARIA, JESUS; BENESH, DANA, RAE) 23 September 2004 (2004-09-23)

D1 discloses compounds and compound groups which are covered by the claimed object. The priority documents have not been checked re Article 33(3) PCT.